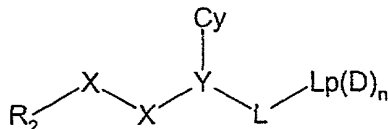


Claims

1. A serine protease inhibitor compound of formula (I)



(I)

wherein:

R₂ is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, MeSO₂- or R₁, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxy, carbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R₂ cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_{1a}, C(R_{1a})₂ or NR_{1a} group, at least one X being C, CO, CR_{1a} or C(R_{1a})₂;

each R_{1a} independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl alkoxyalkyl, alkoxy, carbonyl, alkylaminocarbonyl, alkoxy, carbonyl, amino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R₁ is as defined for R_{1a}, provided that R₁ is not unsubstituted aminoalkyl;

Y (the α -atom) is a nitrogen atom or a CR_{1b} group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, optionally substituted by groups R_{3a} or phenyl optionally substituted by R_{3a} or R_{3i}X_i;

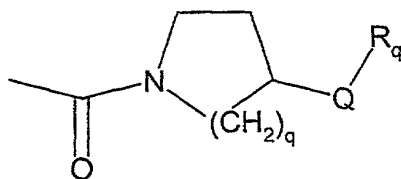
5 each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkyloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a
10 group of the formula -C(X³)N(R¹¹)R¹² (wherein X³ is O or S; and R¹¹ and R¹² are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group), or -OCH₂O- which is bonded to two adjacent ring atoms
15 in Cy;

X_i is a bond, O, NH or CH₂;

R_{3i} is phenyl, pyridyl or pyrimidinyl optionally substituted by R_{3a};

R_{1b}, R_{1c} and R_{1j} are as defined for R_{1a}; and

20 -L-Lp(D)_n is



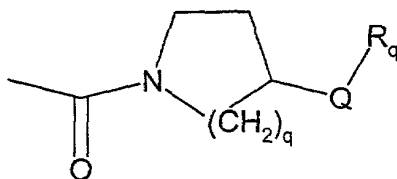
q is 1 or 2;

Q is methylene; and R_q is NR_aR_b in which each of R_a and R_b independently is hydrogen or C₁₋₃alkyl; or one of R_a and R_b is
25 hydrogen or methyl and the other of R_a and R_b is (3-6C)cycloalkyl, pyrid-4-yl, -CH₂-R_c or -CH₂-R_d in which R_c is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, CONH₂, SO₂NH₂, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or
30 methylsulphonyl substituent) and in which R_d is isopropyl or

cyclopentyl, or NR_aR_b is azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino, or tetrahydro-1,4-diazepino [in which a pyrrolidino or piperidino may be a 3,4-didehydro derivative and in which a azetidino,

- 5 pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino, or tetrahydro-1,4-diazepino may be optionally substituted on a ring carbon atom by hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl (provided that the amino, 10 hydroxy or alkoxy substituent is not on a ring carbon atom which is included in a double bond, or adjacent to a ring oxygen, sulfur or nitrogen atom) and in which the piperazino or tetrahydro-1,4-diazepino may bear a methyl group at the 4-position];
- 15 or a physiologically-tolerable salt thereof.

2. A compound according to claim 1 wherein $-\text{L-Lp(D)}_n$ is of the formula:



20 wherein:

q is 1 or 2;

Q is methylene; and R_q is NR_aR_b in which each of R_a and R_b independently is hydrogen or C_{1-3} alkyl; or one of R_a and R_b is hydrogen or methyl and the other of R_a and R_b is $-\text{CH}_2-\text{R}_c$

- 25 or $-\text{CH}_2-\text{R}_d$ in which R_c is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, CONH_2 , SO_2NH_2 , methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and in which R_d is isopropyl or cyclopentyl, or NR_aR_b is
- 30 pyrrolidino, piperidino, morpholino, piperazino, or tetrahydro-1,4-diazepino in which a pyrrolidino or piperidino

may be a 3,4-didehydro derivative and in which a pyrrolidino, piperidino, piperazino, or tetrahydro-1,4-diazepino may bear a methyl group at the 4-position; or a physiologically-tolerable salt thereof.

5

3. A compound according to claim 1 or claim 2 wherein q is 2.

4. A compound according to any of claims 1 to 3 wherein

10 R_q is NR_aR_b in which R_a is hydrogen or C_{1-3} alkyl and R_b is C_{1-3} alkyl; or R_a is hydrogen and R_b is (3-6C)cycloalkyl or pyrid-4-yl; or NR_aR_b is azetidino, pyrrolidino, piperidino, morpholino, thiomorpholino or piperazino [in which a pyrrolidino, piperidino or piperazino may be optionally

15 substituted on a ring carbon atom by hydroxy or hydroxymethyl (provided that the hydroxy substituent is not on a ring carbon atom which is adjacent to a ring nitrogen atom) and in which the piperazino may bear a methyl group at the 4-position].

20 5. A compound according to any of claims 1 to 4 wherein R_q is selected from dimethylamino, diethylamino, prop-2-ylamino, pyrrolidino, 3-pyrrolino, 3-hydroxypyrrolidino, 3-hydroxymethylpyrrolidino, piperidino, 3-hydroxypiperidino, 4-hydroxypiperidino, 4-hydroxymethylpiperidino, piperazino and

25 4-methylpiperazino.

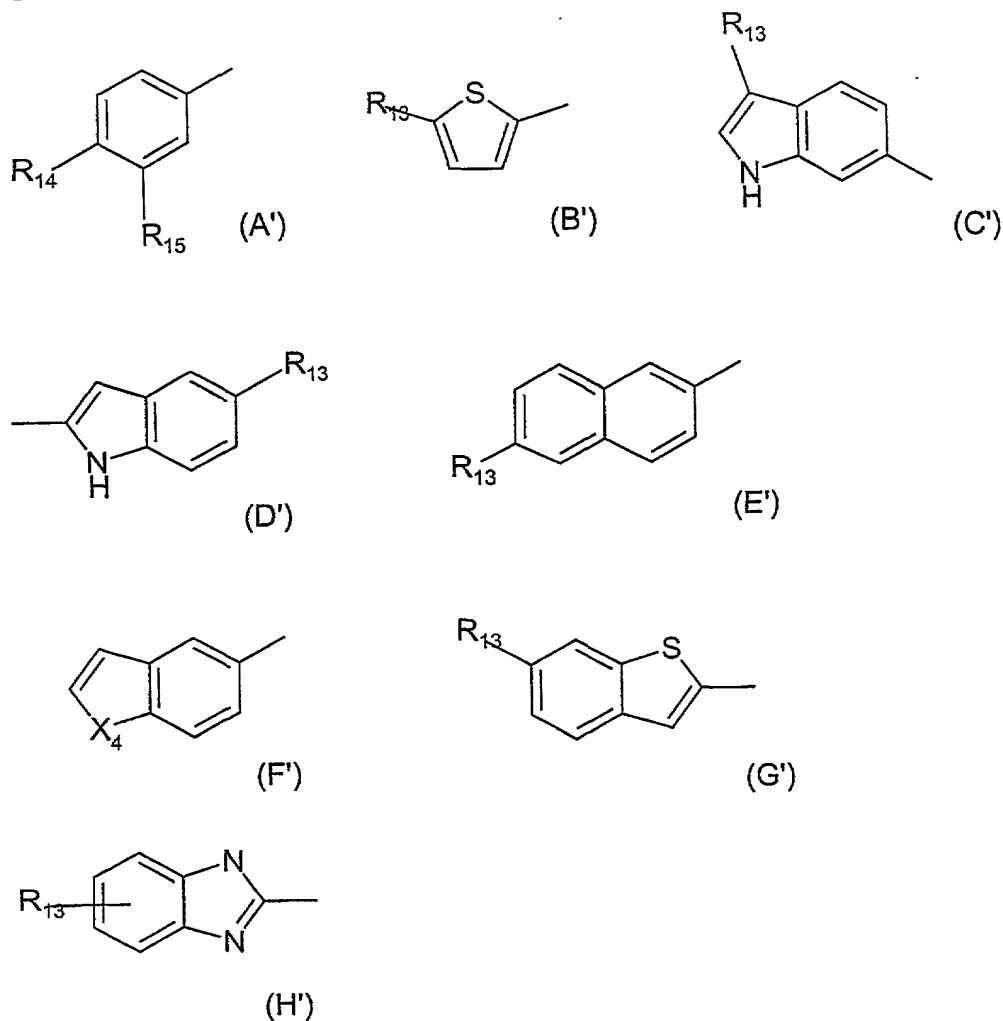
6. A compound according to any one of claims 1 to 5 wherein R_2 is phenyl, thien-2-yl, naphthyl, indol-2-yl, indol-6-yl, benzo[b]furan-5-yl, benzo[b]thiophen-2-yl or benzimidazol-2-yl

30 (each of which is optionally substituted as defined in claim 1).

7. A compound according to any one of claims 1 to 6 wherein optional substituents for R_2 are selected from:

fluoro, chloro, bromo, iodo, nitro, thiol, difluoromethoxy, trifluoromethoxy, hydrazido, methylhydrazido, amino, cyano, trifluoromethyl, methylthio, vinyl, ethynyl, acetylamino, carboxy, acetoxy, hydroxy, methyl, ethyl, amido (CONH₂), aminomethyl, methoxy and ethoxy.

8. A compound according to any one of claims 1 to 5 wherein R₂ is selected from one of the formula (A') to (H'):



wherein X₄ is O or S, R₁₃ is selected from hydrogen, chloro or methyl and R₁₄ is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and R₁₅ is selected from hydrogen, methyl, fluoro, chloro and amino.

9. A compound according to claim 8, wherein R_2 is 4-methoxyphenyl, 5-chloroindol-2-yl, 3-chloroindol-6-yl, indol-6-yl or 3-methylindol-6-yl.

5 10. A compound according to any one of claims 1 to 9 wherein -X-X- is -CONH-.

11. A compound according to any one of claims 1 to 10 wherein Y is CH.

10

12. A compound according to any one of claims 1 to 11 wherein Cy is an optionally R_{3a} substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl, furanyl, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, imidazolyl, 15 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrimidinyl, pyridazinyl, quinoloyl, isoquinolyl, benzofuryl, benzothienyl or cycloalkyl group, or a phenyl group substituted by $R_{3i}X_i$ in which X_i is a bond, O, NH or CH_2 and R_{3i} is phenyl optionally substituted by R_{3a} .

20

13. A compound according to any one of claims 1 to 12 wherein Cy is an optionally R_{3a} substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl or cycloalkyl group.

25

14. A compound according to any one of claims 1 to 13 wherein R_{3a} is selected from hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl),

30

alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, aminoalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxycarbonylamino, amino, halo, cyano, nitro, thiol,

alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S; and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group) and $-OCH_2O-$ which is bonded to two adjacent ring atoms in Cy.

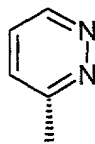
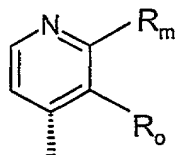
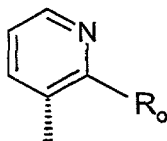
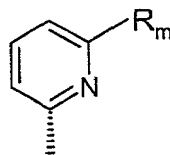
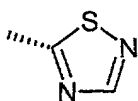
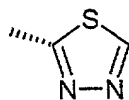
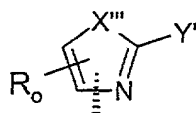
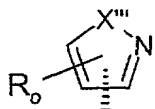
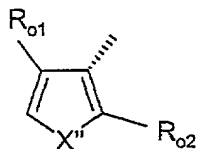
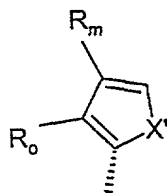
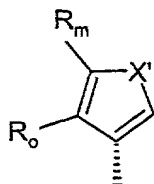
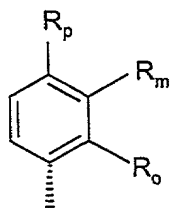
10 15. A compound according to any one of claims 1 to 13 wherein R_{3a} is selected from hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl),
15 alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, aminoalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxycarbonylamino, amino, halo, cyano, nitro, thiol,
20 alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl.

16. A compound according to any one of claims 1 to 15 wherein R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy,
25 methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, $CONH_2$, CH_2CONH_2 , acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro,
30 chloro, bromo, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy, trifluoromethyl, pyrrolidin-1-ylcarbonyl,

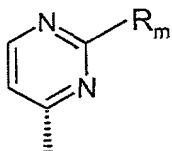
piperidin-1-ylcarbonyl or morpholin-1-ylcarbonyl and $-OCH_2O-$ (which is bonded to two adjacent ring atoms in Cy).

17. A compound according to any one of claims 1 to 16 wherein
5 R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy,
methyl, ethyl, methylaminomethyl, dimethylaminomethyl,
hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl,
ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl,
aminomethyl, $CONH_2$, CH_2CONH_2 , acetylamino, methoxycarbonylamino,
10 ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro,
chloro, cyano, nitro, thiol, methylthio, methylsulphonyl,
ethylsulphonyl, methylsulphenyl, methylsulphonylamido,
ethylsulphonylamido, methylaminosulphonyl,
ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy and
15 trifluoromethyl.

18. A compound according to any one of claims 1 to 11
wherein Cy is selected from:



or



wherein:

X' is selected from O, S and NMe;

5 X'' is selected from O and S;

X''' is selected from O, S, NH and NMe;

Y' is selected from hydrogen, amino and methyl;

R_o is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and

10 methylsulphonyl;

R_m is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the

formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S, and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);

5 R_p is selected from hydrogen and fluoro; or

R_o and R_m or R_m and R_p form an $-OCH_2O-$ group; or

R_o and R_m together with the ring to which they are attached form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroaryl ring contains 1 or 2 heteroatoms selected from

10 nitrogen, oxygen and sulfur); and

one of R_{o1} and R_{o2} is hydrogen and the other is R_o .

19. A compound according to any one of claims 1 to 18 wherein
Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl,
15 4-carbamoylphenyl, pyrid-2-yl, pyrid-4-yl, thien-2-yl, thien-
3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl,
thiazol-4-yl, 2-amino-thiazol-4-yl, thiazol-5-yl, naphth-1-yl,
isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-
yl and quinolin-8-yl.

20

20. A compound as claimed in any one of Claims 1 to 19, in which the alpha atom in Y is carbon and has the conformation that would result from construction from a D- α -aminoacid $NH_2-CR_{1b}(Cy)-COOH$ where the NH_2 represents part of X-X.

25

21. A pharmaceutical composition, which comprises a compound as claimed in any one of claims 1 to 20 together with at least one pharmaceutically acceptable carrier or excipient.

30 22. A compound as claimed in any one of claims 1 to 20 for use in therapy.

23. Use of a compound as claimed in any one of claims 1 to 20

for the manufacture of a medicament for the treatment of a thrombotic disorder.

24. A method of treatment of a human or non-human animal body
5 to combat a thrombotic disorder, which comprises administering
to said body an effective amount of a compound as claimed in
claim 1.

25. A pharmaceutical composition comprising a compound as
10 claimed in any one of claims 1 to 20 for use to combat a
thrombotic disorder.

26. A compound of formula I as claimed in claim 1 and named
in any of the Examples herein, or a physiologically-tolerable
15 salt thereof.